DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Room W-O66-0609
Silver Spring, MD 20993-0002

Mr. Joseph Mazzarella
Senior Manager, Regulatory Affairs
Edwards Lifesciences LLC
One Edwards Way
Irvine, CA 92614

OCT 19 2012

Re: P110021
Edwards SAPIEN™ Transcatheter Heart Valve (Model 9000TFX, sizes 23mm and 26mm) with RetroFlex 3 Delivery System (Models 9120FS23 and 9120FS26), Edwards SAPIEN™ Transcatheter Heart Valve with Ascendra Delivery System (Models 9100BCL23 and 9100BCL26), and accessories (RetroFlex™ Balloon Catheter, Models 9120BC20 and 9120BC23; Ascendra™ Balloon Aortic Valvuloplasty Catheter, Model 9100BAVC; Ascendra™ Introducer Sheath Set Model 9100IS; and Crimper, Models 9100CR23 and 9100CR26)
Filed: May 2, 2011
Amended: May 31, June 10, August 22, and October 11, 2011, February 17, March 21, April 5, April 18, April 25 (two amendments), May 11, May 24, June 29, July 3, July 25 and August 7, 2012
Procode: NPT

Dear Mr. Mazzarella:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for Edwards SAPIEN™ Transcatheter Heart Valve Model 9000TFX, sizes 23mm and 26mm, and Transapical and Transfemoral Accessories listed above. This device is indicated for the following:

Transapical

The Edwards SAPIEN transcatheter heart valve, model 9000TFX, sizes 23 mm and 26 mm, is indicated for transapical delivery in patients with severe symptomatic calcified native aortic valve stenosis without severe aortic insufficiency and with ejection fraction > 20% who have been examined by a heart team including an experienced cardiac surgeon and a cardiologist and found to be operative candidates for aortic valve replacement but who have a Society of Thoracic Surgeons operative risk score $\geq$ 8% or are judged by the heart team to be at a $\geq$15% risk of mortality for surgical aortic valve replacement.

The Ascendra Balloon Catheter is indicated for the transapical delivery of the Edwards SAPIEN transcatheter heart valve.

Transfemoral

The Edwards SAPIEN Transcatheter Heart Valve, model 9000TFX, sizes 23 mm and 26 mm, is indicated for transfemoral delivery in patients with severe symptomatic calcified native aortic valve stenosis without severe aortic insufficiency and with ejection fraction >20% who have been examined by a heart team including an experienced cardiac surgeon and a cardiologist and found to either be: 1) inoperable and in whom existing co-morbidities would not preclude the expected benefit from correction of the aortic stenosis; or 2) be operative candidates for aortic valve replacement but who have a Society of Thoracic Surgeons predicted operative risk score ≥8% or are judged by the heart team to be at a ≥15% risk of mortality for surgical aortic valve replacement.

The RetroFlex 3 Delivery System is indicated for the transfemoral delivery of the Edwards SAPIEN transcatheter heart valve.

We are pleased to inform you that the PMA is approved. You may begin commercial distribution of the device in accordance with the conditions of approval described below.

The sale and distribution of this device are restricted to prescription use in accordance with 21 CFR 801.109 and under section 515(d)(1)(B)(ii) of the Federal Food, Drug, and Cosmetic Act (the act). The device is further restricted under section 515(d)(1)(B)(ii) of the act insofar as the labeling must specify the specific training or experience practitioners need in order to use the device. FDA has determined that these restrictions on sale and distribution are necessary to provide reasonable assurance of the safety and effectiveness of the device. Your device is therefore a restricted device subject to the requirements in sections 502(q) and (r) of the act, in addition to the many other FDA requirements governing the manufacture, distribution, and marketing of devices.

Expiration dating for the Edwards SAPIEN™ Transcatheter Heart Valve and all accessories has been established and approved at 2 years. This is to advise you that the protocol you used to establish this expiration dating is considered an approved protocol for the purpose of extending the expiration dating as provided by 21 CFR 814.39(a)(7).

Continued approval of this PMA is contingent upon the submission of periodic reports, required under 21 CFR 814.84, at intervals of one year (unless otherwise specified) from the date of approval of the original PMA. Two copies of this report, identified as "Annual Report" (please use this title even if the specified interval is more frequent than one year) and bearing the applicable PMA reference number, should be submitted to the address below. The Annual Report should indicate the beginning and ending date of the period covered by the report and should include the information required by 21 CFR 814.84.

In addition to the above, and in order to provide continued reasonable assurance of the safety and effectiveness of the device, the Annual Report must include, separately for each model number (if applicable), the number of devices sold and distributed during the reporting period, including those distributed to distributors. The distribution data will serve as a denominator and provide necessary

context for FDA to ascertain the frequency and prevalence of adverse events, as FDA evaluates the continued safety and effectiveness of the device.

In addition to the Annual Report requirements, you must provide the following data in post-approval study reports (PAS).

You must conduct two post-approval studies to: (1) continue the follow-up of patients from the premarket study through five years post-implant and (2) follow newly enrolled patients in a registry through five years post-implant.

1. *Continue Follow-up of Premarket Cohort:* This study should be conducted as per protocol dated May 2012 Version 5.1, located in PMA Amendment 12. The study will consist of all IDE patients currently enrolled and alive. The objectives of this study are to describe the five-year durability and quality of life outcomes associated with use of the SAPIEN device. Durability will be evaluated using aortic insufficiency as measured via echocardiogram. Quality of life will be measured using the following assessments: KCCQ, SF-12, and EQ-5D Utilities. The surviving patients in the premarket cohort at the time of PMA approval will be followed annually up to five-years.

2. *Newly Enrolled Study:* This study should be conducted as per protocol dated June 2012 Version 1.1, located in PMA Amendment 14. This study will consist of a minimum of 700 patients for high risk Transfemoral patients, and a minimum of 1010 patients for high risk Transapical patients in 35 sites. Sites will be selected to ensure that large volume (>200 valves per year), medium volume (100-200 valves per year) and small volume (50-100 valves per year) are represented in the analysis.

   The objectives of this study are to evaluate: (1) the neurological and vascular outcomes at 30 days and annually through five years post-implant, (2) the learning curve among surgical teams placing the device, and (3) composite safety and effectiveness endpoints at 30 days and annually through five years post-implant.

   For the transfemoral approach, the 30 day and one year evaluation of stroke requires a sample size of 564 and 614 respectively assuming a background incidence risk of 3.75% and 4.17% respectively in order to detect an increase of 0.03.

   For the transapical approach, the 30 day and one year evaluation of stroke requires a sample size of 916 and 730 respectively assuming a background incidence risk of 6.73% and 9.62% respectively in order to detect an increase of 0.03 and 0.04 respectively.

   The data collection for this study (i.e. pre-procedure, peri-procedure, post-procedure, discharge, 30-day, and one-year follow-up) must be nested within the National Transcatheter Aortic Valve Replacement (TVT) registry housed jointly by the American College of Cardiology and Society for Thoracic Surgeons. The long-term follow-up (annually through five years post-implant) will be conducted through linkage of the data to CMS Medicare.

Please be advised that the results from these studies should be included in the labeling as these data become available. Any updated labeling must be submitted to FDA in the form of a PMA Supplement.

FDA would like to remind you that you are required to submit separate PAS Progress Reports for each of the studies every six months during the first two years and annually thereafter. The reports should clearly be identified as Post-Approval Study Report. Two copies for each study, identified as "PMA Post-Approval Study Report" and bearing the applicable PMA reference number, should be submitted to the address below. For more information on post-approval studies, see the FDA guidance document entitled, "Procedures for Handling Post-Approval Studies Imposed by PMA Order"
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070974.htm

Be advised that the failure to conduct any such study in compliance with the good clinical laboratory practices in 21 CFR part 58 (if a non-clinical study subject to part 58) or the institutional review board regulations in 21 CFR part 56 and the informed consent regulations in 21 CFR part 50 (if a clinical study involving human subjects) may be grounds for FDA withdrawal of approval of the PMA.

Before making any change affecting the safety or effectiveness of the device, you must submit a PMA supplement or an alternate submission (30-day notice) in accordance with 21 CFR 814.39. All PMA supplements and alternate submissions (30-day notice) must comply with the applicable requirements in 21 CFR 814.39. For more information, please refer to the FDA guidance document entitled, "Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision-Making Process"
(www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089274.htm).

You are reminded that many FDA requirements govern the manufacture, distribution, and marketing of devices. For example, in accordance with the Medical Device Reporting (MDR) regulation, 21 CFR 803.50 and 21 CFR 803.52, you are required to report adverse events for this device. Manufacturers of medical devices, including in vitro diagnostic devices, are required to report to FDA no later than 30 calendar days after the day they receive or otherwise becomes aware of information, from any source, that reasonably suggests that one of their marketed devices:

1. May have caused or contributed to a death or serious injury; or

2. Has malfunctioned and such device or similar device marketed by the manufacturer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

Additional information on MDR, including how, when, and where to report, is available at www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm.

In accordance with the recall requirements specified in 21 CFR 806.10, you are required to submit a written report to FDA of any correction or removal of this device initiated by you to: (1) reduce a risk to health posed by the device; or (2) remedy a violation of the act caused by the device which may present a risk to health, with certain exceptions specified in 21 CFR 806.10(a)(2). Additional information on recalls is available at www.fda.gov/Safety/Recalls/IndustryGuidance/default.htm.

CDRH does not evaluate information related to contract liability warranties. We remind you; however, that device labeling must be truthful and not misleading. CDRH will notify the public of its decision to approve your PMA by making available, among other information, a summary of the safety and effectiveness data upon which the approval is based. The information can be found on the FDA CDRH Internet HomePage located at www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/PMAApprovals/default.htm. Written requests for this information can also be made to the Food and Drug Administration, Dockets Management Branch, (HFA-305), 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. The written request should include the PMA number or docket number. Within 30 days from the date that this information is placed on the Internet, any interested person may seek review of this decision by submitting a petition for review under section 515(g) of the act and requesting either a hearing or review by an independent advisory committee. FDA may, for good cause, extend this 30-day filing period.

Failure to comply with any post-approval requirement constitutes a ground for withdrawal of approval of a PMA. The introduction or delivery for introduction into interstate commerce of a device that is not in compliance with its conditions of approval is a violation of law.

You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form. Final printed labeling that is identical to the labeling approved in draft form will not routinely be reviewed by FDA staff when accompanied by a cover letter stating that the final printed labeling is identical to the labeling approved in draft form. If the final printed labeling is not identical, any changes from the final draft labeling should be highlighted and explained in the amendment.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing. One of those three copies may be an electronic copy (eCopy), in an electronic format that FDA can process, review and archive (general information: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/ucm134508.htm; clinical and statistical data: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/ucm136377.htm)

U.S. Food and Drug Administration
Center for Devices and Radiological Health
PMA Document Mail Center – WO66-G609
10903 New Hampshire Avenue
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If you have any questions concerning this approval order, please contact Lisa Kennell at (301) 796-6376.

Sincerely yours,

Christy Foreman

Christy Foreman
Director
Office of Device Evaluation
Center for Devices and Radiological Health